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Environmental Tobacco Smoke, Cardiovascular Disease, and the Nonlinear Dose-Response Hypothesis

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Two recent government reports have focused attention on the hypothesis that environmental tobacco smoke (ETS) exposure increases the risk of cardiovascular disease (CVD) in nonsmokers. The first report was published by the California Environmental Protection Agency (CAEPA) in 1997. The second report was issued in 1998 by the Scientific Committee on Tobacco and Health (SCOTH) in the United Kingdom. A meta-analysis of five large prospective epidemiology studies reports that the relative risk for actively smoking 20 cigarettes per day is 1.78. Active smoking exposes the smoker to approximately 16 times the ETS concentration, and 100- to 300-fold the total smoke dose experienced by a nonsmoker (Smith and Ogden, 1998, *JAMA* 280, 32–33.). Despite the much lower smoke exposure, these government reports estimate the relative risk for ischemic heart disease in ETS-exposed nonsmokers at 1.30 (CAEPA) and 1.23 (SCOTH). As an explanation for this nonlinear dose-response anomaly, platelet aggregation is proposed to be a plausible and quantitatively consistent mechanism. Herein, evidence is presented suggesting that this low-dose hypothesis is inconsistent with the biochemistry and physiology of platelets and with the literature on the cardiovascular pathology of active smoking. In addition, several important biases and confounders are ignored. These epidemiologic biases and confounders include the following: misclassification of smokers as nonsmokers; improper use of death certificates as surrogates for mortality statistics; underreporting of diabetes and hypertension in the relatives of smokers; and additional atherogenic risk factors in smoking households. Future field studies on ETS and CVD should emphasize proximal markers of risk for thrombosis in exposed nonsmokers. Proximal thrombogenic risk markers identified in field studies should be mechanistically examined under controlled exposure conditions.

Key Words: environmental tobacco smoke; cardiovascular disease; active smoking; platelet aggregation; dose response; thrombogenesis; atherosclerotic plaque formation.

Two recent government reports and a meta-analysis (He *et al.*, 1999) have focused attention on the hypothesis that environmental tobacco smoke (ETS) exposure increases the risk of cardiovascular disease (CVD) in nonsmokers. The first report was published in September, 1997 by the California Environmental Protection Agency (CAEPA, 1997). The second report was issued the following year by the Scientific Committee on Tobacco and Health (SCOTH) in the United Kingdom (SCOTH, 1998). CAEPA and SCOTH have estimated the relative risk of CVD in nonsmokers exposed to ETS at 1.30 and 1.23, respectively. The meta-analysis of ten cohort and eight case-control studies reports overall findings (relative risk 1.25) similar to these government publications, and reports a surprisingly high relative risk of 1.51 (95% confidence interval, 1.26 to 1.81) for the subgroup of eight case-control studies.

As compared with these relative risks, the relative risk for actively smoking 20 cigarettes per day is estimated by meta-analysis of five large prospective epidemiology studies at 1.78 (Fig. 1) (Law *et al.*, 1997). The prospective epidemiology studies included in the meta-analysis by Law *et al.* (1997) are the following: American Cancer Society Nine State (Hammond and Dorn, 1958); British Doctors (Doll and Hill, 1964, 1966); U.S. Veterans (Kahn, 1966); American Cancer Society 25 State (Hammond, 1966); and the Pooling Project (Pooling Project Research Group, 1978). Law *et al.* (1997) analyzed each of the five studies separately. In each study, smokers were divided into three or four categories by the number of cigarettes smoked. In 10-year age groups, logistic linear regressions of the risk of ischemic heart disease relative to nonsmokers were fitted on the adjusted average number of cigarettes smoked per day in each consumption category. From each regression, the risk of ischemic heart disease associated with smoking one cigarette per day was linearly extrapolated. The average risk for the five studies was determined via weighting by the inverse variance. Because ETS exposure represents only approximately 0.3–1% of the dose of active smoking (Law *et al.*, 1997; Smith and Ogden, 1998), accounting for the disproportionately high CVD risks reported for ETS exposure is problematic.

Law *et al.* (1997) hypothesize a platelet-aggregation mechanism to explain this highly nonlinear dose-response anomaly (Fig. 2). This hypothesis underlies the conclusions reached in both the CAEPA (1997) and SCOTH (1998) reports, influences He *et al.* (1999), and can be synopsized as follows:

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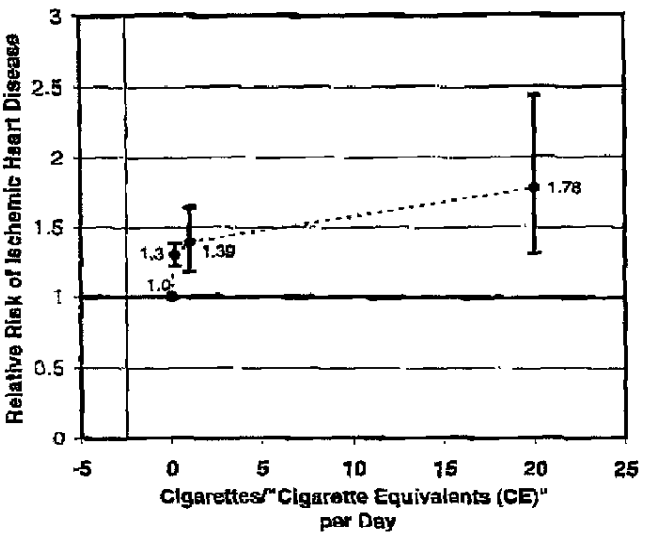

FIG. 1. Nonlinear dose response. The nonlinear relationship between RR and exposure is demonstrated by the failure of these points to lie on a straight line that includes RR = 1 at 0 exposure. The 1.78 and 1.39 RRs are meta-analytic values derived from five large prospective active smoking epidemiology studies (see introductory section of paper). The 1.3 RR is the meta-analytic value for ETS exposure reported by Law *et al.* (1997). Exposure to ETS is expressed in terms of cigarette equivalents (CE) to allow a comparison with the two active-smoking points. The basis of the CE estimate is the exposed nonsmoker plasma-cotinine estimate proposed by Law *et al.* (1997): 1% of 20 cigarettes/day ≈ 0.2 CE/day. Estimates from two recent, very large, demographically representative surveys not cited by Law (Pirkle *et al.*, 1996; Health Survey for England, 1994) suggest that Law's value is an overestimate. In particular, the serum cotinine data presented in these two studies predict nonsmoker exposures of approximately 0.2% to 0.4% (approximately 0.04 to 0.08 CE). Incorporation of either value in the figure would exacerbate the nonlinearity of the relationship. In general, CEs are used as approximate indicators of exposure to ETS. CEs based on markers other than cotinine may be higher or lower. See Phillips *et al.* (1999) and references therein.

Hypothesis: Platelet aggregation provides a plausible and quantitatively consistent mechanism for the low dose effect. The increase in platelet aggregation produced experimentally by exposure to environmental tobacco smoke would be expected to have acute effects increasing the risk of ischemic heart disease by 34%.

The purpose of this review is to evaluate this hypothesis in light of what is known about the cardiovascular effects of both active smoking and ETS. This analysis will also briefly consider differences in cardiovascular risk factors related to lifestyle and socioeconomics, which are more common in smokers and their spouses. An implicit assumption in this analysis is that any direct cardiotoxic effect of ETS exposure in nonsmokers would be expected to be seen in active smokers. This assumption is based on the approximately 16-fold increase in ETS exposure experienced by active smokers compared with nonsmokers (Ogden, 1996). In addition, despite significant physical and chemical differences, ETS and mainstream smoke possess many of the same compounds (Smith *et al.*, 1992), with the active smoker receiving a much higher dose.

In order to analyze mechanistically the ETS/CVD nonlinear dose-response hypothesis, the following questions must be addressed:

Active Smoking

- What role does thrombus formation play in the pathogenesis of a myocardial infarction?
- What role does platelet aggregation play in thrombus formation?

Environmental Tobacco Smoke

- Is platelet aggregation induced by real-world ETS levels?
- Is clinically significant thrombus formation induced by real-world ETS levels?
- Does ETS exposure initiate the formation or exacerbate the growth of atherosclerotic plaques in the coronary arteries?
- Is plaque stability adversely affected by real-world ETS exposure?
- Does ETS exposure increase the risk of myocardial infarction and unstable angina?

By addressing the first six questions, it will be shown that real-world levels of ETS probably do not directly increase the risk of myocardial infarction and unstable angina in exposed nonsmokers. The possible role of sensory-mediated physiologic stress effects on the cardiovascular system of ETS-exposed nonsmokers is briefly addressed.

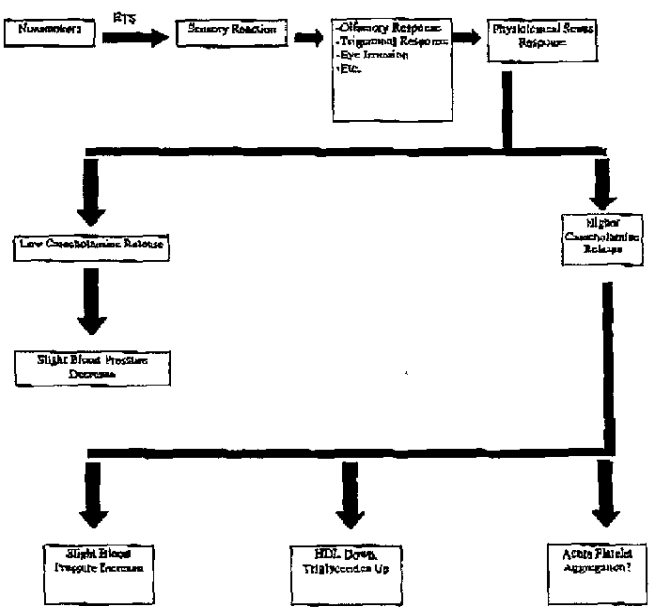

FIG. 2. Sensory-mediated responses to large, acute ETS doses.

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Pathophysiology of Cardiovascular Disease

As a prelude to understanding the unresolved questions surrounding ETS and CVD, a brief summary of current concepts regarding the pathogenesis of myocardial infarction and the sometimes paradoxical cardiovascular pathology of active smoking may be illustrative.

Role of Thrombus Formation in the Pathogenesis of a Myocardial Infarction

Over the last decade, understanding of the mechanistic basis underlying acute myocardial infarction and unstable angina has been revolutionized. Despite this conceptual revolution, much of the basis of clinical cardiology and cardiac surgery rests on an outdated axiom: the greater the stenosis, the greater the risk of an adverse clinical event (Libby, 1995). This axiom is outdated because of the emergence of the following concepts:

- Mechanically and biochemically stable atherosclerotic plaques may narrow the arterial lumen and cause stable angina pectoris but are relatively harmless (Schroeder and Falk, 1995).
- Even in partially unstable plaques, small plaque defects usually do not cause clinical events. Examples of small defects would include plaque erosions (superficial intimal injury) and modest fissures with overlying microscopic mural thrombosis (Fishbein and Siegel, 1996).
- Due to compensatory enlargement of arteries with atherosclerosis, luminal inner diameter of the vessel remains normal until approximately 40% of the arterial cross-section is occupied by plaque. This occurrence is referred to as the Glagov phenomenon (Glagov *et al.*, 1987).
- It is large unstable plaques, which do not produce significant stenosis because of remodeling, that rupture and form occlusive thrombosis, resulting in myocardial infarction and unstable angina (Fishbein and Siegel, 1996).
- Vulnerable plaques prone to rupture are characterized by a thin, fibrous cap infiltrated by macrophages (Burke *et al.*, 1998).
- During an acute myocardial infarction, blood flow to the myocardium can be intermittent due to the competing processes of thrombosis and thrombolysis (Schroeder and Falk, 1995).
- Inflammatory processes are important in the pathogenesis of an acute myocardial infarction. Accumulations of mast cells (200-fold more than in the unaffected coronary intima) develop at the site of occlusive atheromatous erosion or rupture (Kovanen *et al.*, 1995). In addition, interleukin-1β is present in luminal and advential vessel endothelial cells and macrophages in coronary arteries from patients with ischemic heart disease (Galea *et al.*, 1996).

Implications of myocardial infarction mechanisms vis-à-vis ETS. Given what is currently known about the causes of a myocardial infarction, what effects would ETS exposure need to elicit to increase risk? The answer to this question requires the separation of two issues. The first issue is whether ETS can initiate cardiovascular disease, i.e., cause plaque formation. The second issue is whether ETS exposure could exacerbate preexisting cardiovascular disease. Exacerbation could take several forms, including but not limited to the following: growth enhancement of dietary-, hemodynamic-, or otherwise-induced plaque; destabilization of preexisting plaque, e.g., increase in inflammatory infiltrate; increased tendency to develop thrombus; decrease in thrombolysis; or increase in vasospasm of an atherosclerotic vessel (Meredith *et al.*, 1993).

Role of Platelet Aggregation in Thrombus Formation

Central to the hypothesis stated in the first section is the role of the platelet in thrombosis. Coronary thrombi are rich in platelets. These platelets can be activated either directly by shear forces on exposed plaque components, or indirectly through thrombin generation (Schroeder and Falk, 1995). In patients with acute coronary syndromes, the data suggest that thrombin is generated via the intrinsic (contact activation) coagulation pathway (Hoffmeister *et al.*, 1995; Merlini *et al.*, 1994). If this suggestion is correct, then monocyte tissue factor may be important in initiating thrombosis after plaque disruption (Fernandez-Ortiz *et al.*, 1994). Mechanical forces may also contribute, as the greater the stenosis and coarser the arterial surface, the more platelets tend to aggregate and deposit (Falk, 1983; Fernandez-Ortiz *et al.*, 1994; Folts, 1991).

Under nonpathologic circumstances, *in vivo* coagulation and platelet activation are normal physiologic processes essential for maintaining homeostasis. Platelets are affected by activating agents in a dose-dependent manner with reversible responses at lower doses and irreversible activation occurring at higher agonist concentrations (Winslow *et al.*, 1987). Both reversible and irreversible platelet activation occur in normal individuals without cardiovascular diseases.

Reversible platelet activation (or priming) can be elicited by epinephrine or norepinephrine (Larsson *et al.*, 1989; Larsson *et al.*, 1990; Siess, 1989) and occurs in response to routine daily stresses. For example, the psychological pressure associated with performing mental arithmetic (Grignani *et al.*, 1991), taking an examination (Mest *et al.*, 1982), giving a presentation (Arkel, 1977), hearing a loud sound (Andres *et al.*, 1993), being confused (Larsson *et al.*, 1989), and receiving bad news (Rostrup *et al.*, 1990) have all been reported to potentiate platelet activation. In addition, exercise has also been reported to enhance platelet activation (Burghuber *et al.*, 1981; Wang *et al.*, 1994).

Evidence for irreversible platelet activation in normal individuals is provided by the observation that a fraction of platelets circulate as microaggregates (Amodeo *et al.*, 1980) and display the P-selectin marker for degranulation (Tanque *et al.*, 1992). Although the *in vivo* cause of irreversible platelet activation is unknown, it may occur in response to endothelial stress from rheological shear forces and/or inflammatory processes.

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Active smoking and cardiovascular disease. A voluminous literature suggests that the major clinical cardiovascular risk factor associated with active smoking is an increased tendency toward thrombosis (Barbash *et al.*, 1993; Mueller *et al.*, 1992). This tendency may increase the risk of both myocardial infarction and ischemic stroke, due to occlusion of the carotid arteries (American Heart Association, 1998). Myocardial infarction will be discussed here because it is responsible for the majority of cardiovascular deaths (American Heart Association, 1998) and has been the focus of concerns by regulatory bodies.

The following points summarize the active smoking literature:

- In hyperlipidemic populations, e.g., the United States, smoking is associated with increased atherosclerosis (Roberts, 1989).
- The abdominal aorta and the carotid arteries are reportedly affected more than the coronary arteries (McGill, 1988; McGill *et al.*, 1997). The average increase in coronary artery atherosclerosis in smokers is approximately 25% (McGill, 1988). In fact, a recent publication from the Pathologic Determinants of Atherosclerosis in Youth (PDAY) study (McGill *et al.*, 1997) reports no effect of smoking on the extent of either fatty streaks or raised coronary lesions in the right coronary artery. This result was determined from autopsies of 1079 men and 364 women in the 25- to 34-year age group.
- Other results from the PDAY study (1990) suggest that the increase in smoking-associated atherosclerosis may be related to inflammatory processes. This suggestion is based on the observation that young smokers with the same blood serum cholesterol levels as age-matched nonsmokers display increases in abdominal atherosclerosis. The possible role of inflammation is an important point that will be separately discussed in the subsequent text.
- The relatively small increase in coronary atherosclerosis is not sufficient to account for the approximately 2-fold increase in myocardial infarction seen in heavy smokers (McGill, 1988).
- Smokers display increases in blood coagulability (McKarns *et al.*, 1995).
- In summary, the combination of modest increases in coronary artery atherosclerosis and increased tendency toward thrombosis is believed to underlie the increased myocardial infarction risk reported in smokers (Molstad, 1991).

Plausibility of ETS-Induced Platelet Aggregation

Returning to the main topic, we ask whether it is plausible that real-world ETS exposures could, by a mechanism of platelet aggregation, increase the risk of myocardial infarction in nonsmokers by an amount similar to that found in active smokers. If it is not plausible, then is there an alternative explanation for the similarity in reported relative risks for CVD across such a wide range of smoke dose exposures? To this end we first investigate whether very small concentrations of ETS would be expected to elicit platelet aggregation to approximately the same degree seen in active smokers, who experience 100- to 300-fold more smoke exposure (Smith and Ogden, 1998). At least two reasons suggest that a similar degree of platelet response would not be expected.

Dose-response behavior in platelets. First, there is a significant literature that reports monotonic increasing (often sigmoidal) dose-response curves for the aggregation of platelets. This holds for stimulation by a variety of agonists across a wide range of concentrations. For example, Winslow *et al.* (1987) report a sigmoidal dose-response curve for the aggregation of platelets in the presence of platelet-activating factor (PAF), measured at agonist concentrations across a 100,000-fold range. Schmaier (1987) has observed sigmoidal dose response of platelets following stimulation by both collagen and ionophore A23187. Moreover, Feinstein *et al.* (1985) have reported increases in platelet aggregation as a function of increasing concentration of thrombin. In summary, aggregating platelets behave like many other cell types in displaying increased biologic activity with increasing stimulation by agonists (Ross, 1995). Therefore, the much lower smoke exposure associated with ETS as compared with active smoking would be expected to elicit significantly less platelet activation.

Mechanism of platelet aggregation in active smoking. The second reason that platelets would probably not be induced to aggregate at the low ETS concentrations usually encountered by exposed nonsmokers is based on the mechanism by which active smoking is believed to accentuate acute platelet activation. Most likely, the mechanism is related to sensitization of the platelet by nicotine-induced release of epinephrine. Exposure of the platelet to epinephrine increases the tendency toward aggregation in the presence of agonists, e.g., ADP, collagen, thrombin, PAF, etc. (Smith *et al.*, 1998).

How much exposure to nicotine do nonsmokers receive from ETS? Serum nicotine concentrations between 0.9 and 2.8 ng/ml have been reported following ETS exposure (Biber *et al.*, 1987; Davis *et al.*, 1989; Jarvis *et al.*, 1983; Scherer *et al.*, 1990). Baseline serum nicotine concentration for controls not exposed to ETS is approximately 1 ng/ml. These concentrations are below the threshold of 3 ng/ml for measurable hemodynamic effects (Andersson *et al.*, 1993; Benowitz *et al.*, 1982; Goldsmith *et al.*, 1989; Netscher *et al.*, 1995) (Fig. 3).

It should be noted that there are at least three problems associated with measuring low levels of serum nicotine. First, the gas chromatographic methods utilized are near the level of detection, i.e., 1–2 ng/ml. Biber *et al.* (1987) compared serum nicotine levels measured by gas chromatograph from five laboratories in both ETS-exposed and control subjects. Reported values for a *single* subject ranged from 0.2 to 9.6 ng/ml with an average of 2.8 ng/ml. Secondly, ETS exposure based on self reporting can be skewed by misclassified subjects who can have mainstream exposure nicotine levels from 10 to 30 ng/ml

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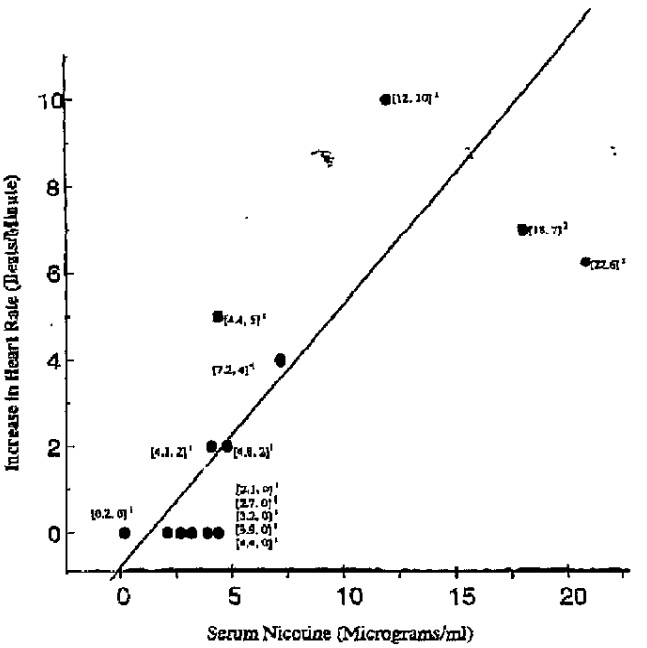

FIG. 3. Response of heart rate to nicotine. Increase in heart rate as a function of serum nicotine concentration from injection (Andersson *et al.*, 1993)[1], nicotine gum (Nerscher *et al.*, 1995)[2], or cigarette smoking (Goldsmith *et al.*, 1989)[3].

(Jarvis *et al.*, 1987, 1989). Finally, nicotine naturally occurring in foods can contribute to baseline values (Davis *et al.*, 1991).

In summary, smoking-related acute platelet aggregation probably results from sensitization of platelets by epinephrine released by the adrenals following nicotine binding to specific receptors (Cryer *et al.*, 1976; Smith *et al.*, 1998). The serum nicotine levels in nonsmokers following ETS exposure are probably not sufficient to stimulate the release of hemodynamically or biochemically significant amounts of epinephrine.

Inflammation and Antioxidants

Atherogenic lifestyle. Cigarette smokers as a group have lifestyles in addition to their smoking that put them at greater risk for chronic disease than nonsmokers (Blair *et al.*, 1980; Cress *et al.*, 1994; Edington, 1988; Lazarus *et al.*, 1989; Shibata *et al.*, 1989; Thompson and Warburton, 1993; Whichelow *et al.*, 1988). Smokers reportedly differ from nonsmokers in many aspects including the following: less educated; attend church less frequently; more likely to have spouses who smoke; more physically active on the job; less likely to eat breakfast and desserts; consume more soft drinks, alcoholic beverages and coffee; sleep less; and have higher pulse rates (men only) and thicker skinfolds. Smokers comprise those occupational groups and social strata with increased exposure to hazards in the workplace, including dust, fumes, and toxic substances (Sterling and Weinkam, 1990).

Many studies have examined smokers' diets. Smokers consume more calories from saturated fat, fewer grams of fiber, fewer fruits and vegetables, and fewer daily micronutrients including vitamin A, vitamin C, retinol, α-tocopherol and iron (Emmons, *et al.*, 1995; Hirayama, 1984; Midgette, *et al.*, 1993). This dietary pattern increases risk for atherosclerosis and coronary heart disease. In addition, Oliver (1989) has suggested that smokers have a reduced intake of the polyunsaturated fatty acid linoleic acid. Low levels of linoleic acid in fat tissue are associated with increased coronary risk at both population and individual levels (Oliver, 1989). Finally, smokers exercise significantly less than nonsmokers (Lazarus *et al.*, 1989).

The lifestyle and socioeconomic risk factors found in smokers are also prevalent in nonsmoking spouses of smokers. For example, familial aggregation in physical fitness (Perusse *et al.*, 1987) and increased concordance of physical activity for married versus surrogate pairs (Venters *et al.*, 1984) have been observed, suggesting that the spouses of smokers may exercise less than spouses of nonsmokers. There are also significant dietary differences between the spouses of smokers and the spouses of nonsmokers (Knutsen and Knutsen, 1989; Koo *et al.*, 1988; Rylander, 1999). Intakes of β-carotene, a good marker for vegetable consumption, were reported to be inversely related to ETS exposure (Marchand *et al.*, 1991). Likewise, self-reported mean dietary intake of β-carotene is lower in nonsmokers exposed to ETS at home than in nonsmokers not exposed to ETS at home (Sidney *et al.*, 1989). The exposed subgroup in the Sidney study also had slightly higher mean body mass index despite its considerably lower average age. Diets of nonsmokers living with smokers were also found to include more calories from fat, fewer grams of fiber, more alcohol, fewer fruits and vegetables, fewer vitamin supplements, and fewer daily micronutrients (Emmons *et al.*, 1995; Matanoski *et al.*, 1995). The dietary differences between the spouses of smokers and the spouses of nonsmokers are to be expected considering the concordance of husband-wife dietary practices (Lindsted and Kuzma, 1990). Therefore, smokers and their nonsmoking spouses share an increased risk for CVD compared with the nonsmoking population because of concordant lifestyle-associated risk factors.

Free radicals. In addition to a reduced intake of dietary antioxidants, smokers are also exposed to free radicals from both cigarette smoke and increased pulmonary inflammation (Pittilo and Woolf, 1994). The possible importance of free radicals in cardiovascular health was demonstrated by improvement in endothelium-dependent vasomotion with cholesterol-lowering antioxidant therapy (Anderson *et al.*, 1995).

Possible influence of lifestyle on thrombogenesis. Lifestyle is usually considered in regard to atherosclerosis because of potential effects on cholesterol metabolism. However, we have

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collected preliminary evidence that suggests lifestyle may also influence the tendency toward thrombogenesis. In an intensive hematologic study on healthy subjects following lifestyles with minimal cardiovascular risk factors other than smoking, thrombogenic risk was less than that previously reported for smokers (McKarns *et al.*, 1995). Although some cardiovascular risk factor increases in the smokers were noted, they were smaller than previously reported. Among males, the following differences between smokers and nonsmokers were noted: white blood cell counts, +26%; fibrinogen levels, +17%; mean corpuscular hemoglobin, +5%; mean corpuscular volume, +4%. In addition, prothrombin time was decreased by 5%. Among females, the only thrombogenic risk factor that differed significantly was the white blood cell count (+43% in the smokers). In this study no atherogenic risk factor differed between smokers and nonsmokers, including cholesterol, low-density lipoprotein, high-density lipoprotein, very low-density lipoprotein, triglycerides, and glucose.

Clinically Significant Thrombus Formation and ETS Levels

In an environmental chamber study using fresh diluted sidestream cigarette smoke (FDSS) at a concentration of 179 $\mu g/m^3$ respirable particulate matter (RSP) for 7.33 hours (Smith *et al.*, 1996), several measurements related to blood clotting and viscosity were unchanged by exposure. These measurements included fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hematocrit, hemoglobin, number of red blood cells (RBC), and number of white blood cells (WBC). The only potentially thrombotic measurement that changed in an exposure-related manner was the platelet count, which decreased significantly on the exposure day.

Possible Indirect (Sensory) Effects of Large Acute ETS Exposures

Elucidating the cardiovascular effects of odors may facilitate interpretation of results from ETS studies. In the environmental chamber study described above (Smith *et al.*, 1996), several changes in blood lipid measurements were observed in both male and female subjects. Among male subjects, triglyceride levels increased by 15%, whereas high-density lipoprotein (HDL) levels decreased by 4.8%. Such lipoprotein changes are consistent with a stress-related catecholamine-induced mobilization of free fatty acids and concomitant decrease in HDL (Nikkila, 1984). This suggests that the observed cardiovascular alterations may have been affected by sensory-mediated stress reactions.

Because many types of stressful stimuli can induce catecholamine release (Wilson and Foster, 1985), it is possible that the odor strength and/or sensory irritation of this acute exposure to a relatively high level of cigarette smoke (252 times the median U.S. smoking workplace ETS exposure level) (Jenkins *et al.*, 1996) elicited norepinephrine release in these ETS-naïve individuals. Unfortunately, an odor only control, e.g., propionic acid, was not conducted in this environmental chamber study (Walker *et al.*, 1999) to determine if dose-related cardiovascular alterations would result.

In a field study conducted on 19 ETS-exposed and 9 nonexposed waitresses, Moffatt *et al.* (1995) also observed decreases in HDL levels in the exposed group. These authors reported an overall decrease in HDL cholesterol of 14% in the ETS-exposed group as compared to the nonexposed group. Similarly, Valkonen and Kuusi (1998) have also reported changes in low-density lipoprotein in blood samples taken from 10 ETS-exposed nonsmokers. This group reported decreases in serum ascorbic acid and serum antioxidant defense, and a reduced capacity of LDL to resist oxidation. Although ETS-associated changes in cholesterol levels are mechanistically interesting, data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY Research group, 1990) multicenter study suggest that the small cholesterol level differences between active smokers and nonsmokers (Craig *et al.*, 1989) are probably not clinically significant *vis-à-vis* coronary artery disease.

ETS and Atherosclerotic Plaque Stability

The data on plaque stability in relation to both active smoking and ETS are limited. The following discussion attempts to summarize and connect a body of poorly understood results. First, in our environmental chamber exposure study (Smith *et al.*, 1996), serum levels of the inflammatory mediators leukotriene B_4 (LB_4) and prostaglandin E_1 (PGE_1) increased 42% and 40%, respectively, on the exposure day. These levels returned to pre-exposure values on the next clean-air day. Interleukin-1, believed to be important in plaque inflammation (Galea *et al.*, 1996), did not change as a result of ETS exposure. Basophils also did not appear to change with exposure. Whether this phenomenon is related to mast cell infiltration in plaque (Kovanen *et al.*, 1995) is unknown.

The consistent observation that peripheral white blood cell count is elevated in active smokers is also difficult to directly relate to plaque stability. Budde and Schaefer (1989) examined the bone marrow of 32 cigarette smokers collected by trephine biopsies (performed because of mild peripheral leukocytosis). In all biopsy samples, they found a moderate to significant increase in granulopoietic cells and stimulation of phagocytic activity in macrophages, with neutrophils being the major target for phagocytosis. These authors interpreted this result as a smoking induced inhibition of locomotion in segmented neutrophils leading to an accumulation of mature polymorphs in the bone marrow, with consecutive breakdown and phagocytosis of senescent cells. The mechanism of this smoking-induced inhibition and the process by which granulopoietic cells increase are unknown.

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The macrophage white blood cell population has been directly compared in the developing atherosclerotic lesions of young smokers and nonsmokers. Botti *et al.* (1996) have demonstrated greater macrophage foam cell populations in 216 quantitative measurements taken from 27 autopsied PDAY cases. The relationship between the peripheral white blood cell count and this observation is also unknown.

Potential physiologic stress effects may interfere with experiments on ETS and white blood cells. Specifically, a significant portion of the WBC population adheres to the blood vessel wall through a process termed margination. Epinephrine release initiates demargination, whereby the measured peripheral WBC count increases, whereas the actual total population remains unchanged (Brenner *et al.*, 1998). Because epinephrine release may result from multiple stimuli, including fear of needles, fear of ETS, or an unpleasant sensory response to ETS, it is difficult to interpret ETS-associated changes in peripheral WBC count. In our chamber study we did not observe changes in peripheral WBC at 179 $\mu g/m^3$ RSP for 7.33 hours (Smith *et al.*, 1996).

Alternative Hypothesis: Influence of Biases and Confounders

Does ETS exposure increase the risk of myocardial infarction and unstable angina? Our recent pilot study (Smith *et al.*, 1998) of 21 ETS-exposed nonsmokers suggests that real-world concentrations of ETS may not aggregate platelets. If this result holds in general, then the putative mechanism of increased CVD risk proposed by Law and others is spurious. The disproportionately high relative risk for CVD reported in Law's meta-analysis of 18 epidemiologic studies must then have another explanation. A far more likely and far less speculative explanation lies in the numerous biases and confounders reported in the ETS/CVD literature. A selection of biases and confounders in CVD in epidemiology studies follows:

- Smokers incorrectly classified as nonsmokers.
- Large error rate introduced through use of death certificates as surrogates for mortality statistics.
- Fewer medical records and less medical care in smoker families.
- Underreporting of diabetes and hypertension in smokers and their relatives.
- Smokers and their families have more atherogenic risk factors.

Among those of particular relevance to this question are the following: misclassification bias, whereby smokers are incorrectly classified as nonsmokers (Ogden *et al.*, 1997; Wagenknecht *et al.*, 1992); underreporting of diabetes and hypertension (ADA, 1997; AHA, 1998; Connolly and Kesson, 1996; Duenas, 1998; Mackenbach *et al.*, 1996); and diagnostic flaws.

Diagnostic flaws. There are at least two major diagnostic flaws that adversely affect the premises upon which the epidemiology studies on ETS and CVD are based: death certificate errors and smoker lifestyle confounding. First, causes of death listed on death certificates are used as surrogates for mortality statistics. A comprehensive review of the literature comparing the accuracy of death certificate data with autopsy and medical record–validated causes of death demonstrates a large error rate on the death certificates (Smith *et al.*, 1998). This large death certificate error rate for CVD is propagated, without critique or compensation, throughout the calculation of a very small increase in relative risk associated with ETS. Second, these epidemiology studies ignore a diagnostic inaccuracy operant against smokers and their spouses. On a comparative basis, this smoker-lifestyle confounder tends to underestimate the incidence of CVD during the lifetime of the smoker and his/her spouse. Conversely, the incidence of CVD, particularly myocardial infarction, is overestimated at death in this group. A major influence underlying this diagnostic inaccuracy is the relative absence of information concerning CVD in smokers and their spouses as compared with nonsmokers, due to socioeconomic, geographic and psychological factors in smoking households (Smith *et al.*, 1998).

DISCUSSION

In 1950 the first series of large retrospective, case-control studies on lung cancer and cigarette smoking were published. Since that time, a number of compounds and families of compounds in tobacco smoke have been proposed as causative agents (Huber, 1989). None of these hypotheses have become widely accepted because of recognition of potential interactive effects within the complex mixture and shortfalls in mechanistic understanding.

Similarly, an attempt to attribute epidemiologically reported increases in cardiovascular risk in ETS-exposed nonsmokers to platelet aggregation is a speculative oversimplification of a very complex issue. First, the reported increases in CVD risk may not be real because of several important potential flaws inherent in the epidemiologic methodology. Second, if the reported increases in risk of between 23 to 30% are real, these increases may be due to biases and confounding factors other than ETS exposure. Third, if the reported increases in risk were both real and related to ETS exposure, the effect may be indirect and therefore attributable to many other stimuli as well. In other words, platelet aggregation is but one piece of a large mechanistic puzzle underlying an adverse cardiovascular event.

Much further work in the form of field studies and exposure chamber studies is required to clarify whether real-world ETS levels constitute a clinically significant risk for CVD in nonsmokers. Given the sensitivity of modern measurement and data analysis methods for detecting small physiologic and biochemical changes in humans, the categorization of a risk as clinically significant should be thoughtfully considered. Perspective on the clinical significance of a measured change in exposed nonsmokers can be attained by considering the repro-

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ducibility, magnitude, directionality, potential for reversibility, and possibility of adaptation. Proper consideration of these factors can allow the results of a series of carefully controlled studies to suggest whether a change is likely to be a negative health effect, a risk factor for the future development of a negative health effect, a temporary adverse change to which the body will adapt, or an inconsequential change within the normal homeostatic range.

In general, changes likely to be more serious would necessarily have the following characteristics: occur at ETS exposure levels encountered in the real world, be reproducible either within an individual test subject or within a subject population, move baseline biochemical or physiologic values outside of the normal clinical range, move baseline values toward increased risk levels in a manner mechanistically consistent with biologically plausible alterations in cardiovascular pathology, display sensitization with increasing exposure, and not display adaptation or reversibility.

Several basic questions should be asked before accepting the conclusions of the CAEPA (1997) and SCOTH (1998) reports. These conclusions are based on the underlying assumptions of Law *et al.* (1997) and lead to the following relative risks in nonexposed individuals for ischemic heart disease: ETS exposure, 1.23; smoking one cigarette per day, 1.39; and actively smoking 20 cigarettes per day, 1.78 (Fig. 1). First, are these results consistent with the known cardiovascular pathology of cigarette smoking? Second, are they consistent with the biochemistry and physiology of platelets? Third, do they take into account the demographic, behavioral, and socioeconomic literature on smokers and their families? The current data suggests that the answer to all three questions is probably no. More definitive answers are likely to emerge as biochemical and epidemiologic understanding grows through carefully focused research. In particular, data on the cardiovascular effects of odors and irritants is rapidly expanding as the results of additional field and chamber studies become available.

REFERENCES

American Diabetes Association. (1997). Diabetes facts and figures. http://www.diabetes.org/ada/c20f.html.

American Heart Association. (1998a). High blood pressure statistics. http://www.amhrt.org/Heart_and_Stroke_A_Z_Guide/hbps.html.

American Heart Association. (1998b). Stroke (brain attack) statistics. http://www.Americanheart.org/Heart_and_Stroke_A_Z_Guide/strokes.html.

Amodeo, P., Angelico, F., Arca, M., and Ricci, G. (1980). Circulating platelet aggregates in an adult population sample. Relationships with the main coronary risk factors and cardiovascular diseases. *Atherosclerosis* **35**, 375–381.

Anderson, T. J., Meredith, I. T., Yeung, A. C., Frei, B., Selwyn, A. P., and Ganz, P. (1995). The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N. Engl. J. Med.* **332(8)**, 488–493.

Andersson, K., Eneroth, P., and Arner, P. (1993). Changes in circulating lipid and carbohydrate metabolites following systemic nicotine treatment in healthy men. *Int. J. Obes. Related Metab. Disord.* **17**, 675–680.

Andres, L., Wadenvik, H., Kutti, J., and Hansson, L. (1993). Stress and platelet activation. *Acta. Haemat.* **70**, 302–306.

Arkel, Y., Heft, J., Kreutner, W., Sherwood, J., and Williams, R. (1977). Alteration in second phase platelet aggregation associated with an emotionally stressful activity. *Thromb. Haemost.* **38**, 552–561.

Barbash, G. I., White, H. D., Modan, M., Diaz, R., Hampton, J. R., Heikkila, J., Kristinsson, A., Moulopoulos, S., Paolasso, E. A. C., Van der Werf, T., Pehrsson, K., Sandoe, E., Simes, J., Wilcox, R. G., Verstraete, M., von der Lippe, G., and Van der Werf, T. (1993). Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. *Circulation* **87**, 53–58.

Benowitz, N., Jacob, P., III, Jones, R., and Rosenberg, J. (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *J. Pharmacol. Exp. Ther.* **221**, 368–372.

Biber, A., Scherer, G., Hoepfner, I., Adlkofer, F., Heller, W., Haddow, J., and Knight, G. (1987). Determination of nicotine and cotinine in human serum and urine: an interlaboratory study. *Toxicol. Lett.* **35**, 45–52.

Blair, A., Blair, S.N., Howe, H. G., Pane, R. R., Rosenberg, M., Parker, G. M., and Pickle, L. W. (1980). Physical, psychological, and sociodemographic differences among smokers, exsmokers, and nonsmokers in a working population. *Prev. Med.* **9(6)**, 747–749.

Botti, T. P., Amin, H., Hiltscher, L., and Wissler, R. W. (1996). A comparison of the quantitation of macrophage foam cell populations and the extent of apolipoprotein E deposition in developing atherosclerotic lesions in young people: high and low serum thiocyanate groups as an indication of smoking. PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. *Atherosclerosis* **124**, 191–202.

Brenner, I., Shek, P. N., Zamecnik, J., and Shephard, R. J. (1998). Stress hormones and the immunological responses to heat and exercise. *Int. J. Sports. Med.* **19(2)**, 130–143. Review.

Budde, R., and Schaeffer, H. E. (1989). Smokers' dismyelopoiesis-bone marrow alterations associated with cigarette smoking. *Pathol. Res. Pract.* **185**, 347–350.

Burghuber, O., Sinzinger, H., Silberbauer, K., Wolf, C., and Haber, P. (1981). Decreased prostacyclin sensitivity of human platelets after jogging and squash. *Prostaglandin Med.* **6**, 127–130.

Burke, A. P., Farb, A., Malcom, G. T., Liang, Y., Smialek, J., and Virmani, R. (1998). Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation* **97**, 2110–2116.

California Environmental Protection Agency (1997). Health effects of exposure to environmental tobacco smoke: cardiovascular health effects. Office of Environmental Health Hazard Assessment, Sacramento, CA. **8**, 1–74.

Connolly, V. M., and Kesson, C. M. (1996). Socioeconomic status and clustering of cardiovascular disease risk factors in diabetic patients. *Diabetes Care* **19(5)**, 419–422.

Craig, W. Y., Palomaki, G. E., and Haddow, J. E. (1989). Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ.* **298(6676)**, 784–788.

Cress, R. D., Holly, E. A., Aston, D. A., Ahn, D. K., and Kristiansen, J. J. (1994). Characteristics of women nonsmokers exposed to passive smoke. *Prev. Med.* **23**, 40–47.

Cryer, P., Haymond, M., Santiago, J., and Shah, S. (1976). Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *N. Engl. J. Med.* **295**, 573–577.

Davis, J., Shelton, L., Watanabe, I., and Arnold, J. (1989). Passive smoking affects endothelium and platelets. *Arch. Intern. Med.* **149**, 386–389.

Davis, R., Stiles, M., DeBethizy, J., and Reynolds, J. (1991). Dietary nicotine: a source of urinary cotinine. *Food Chem. Toxicol.* **29**, 821–827.

Doll, R., and Hill, A. B. (1964). Mortality in relation to smoking: ten years' observations on British doctors. *BMJ.* **1**, 1399–1410.

PM3006532286

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Doll, R., and Hill, A. B. (1966). Mortality of British doctors in relation to smoking; observations on coronary thrombosis. In *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. (W. Haenszel, Ed.). Bethesda MD: U.S. Department of Health, Education, and Welfare. 127–204. (National Cancer Institute Monograph No. 19).

Duenas, M. R. (1998). Tobacco smoke and atherosclerosis progression. *JAMA*. **280(1)**, 32; discussion 33.

Edington, D. W. (1988). University of Michigan study confirms links between smoking and poor health habits. Ann Arbor: University of Michigan News and Information Services.

Emmons, K. M., Thompson, B., Feng, Z., Hebert, J. R., Heimendinger, J., and Linnan, L. (1995). Dietary intake and exposure to environmental tobacco smoke in a worksite population. *Eur. J. Clin. Nutr.* **49**, 336–345.

Falk, E. (1983). Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br. Heart J.* **50**, 127–134.

Feinstein, M. R., Zavoico, G. B., and Halenda, S. P. (1985). Calcium and cyclic AMP: Antagonistic modulators of platelet function. In *Platelets: Physiology and Pharmacology* (G. L. Longenecker, Ed.). pp 237–264. Academic Press.

Fernandez-Ortiz, A., Badimon, J. J., Falk, E., Fuster, V., Meyer, B., Mailhac, A., Weng, D., Shah, P. K., and Badimon, L. (1994). Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J. Am. Coll. Cardiol.* **23**, 1562–1569.

Fishbein, M. C., and Siegel, R. J. (1996). How big are coronary atherosclerotic plaques that rupture? *Circulation* **94(10)**, 2662–2666.

Folts, J. (1991). An *in vivo* model of experimental arterial stenosis, intimal damage, and periodic thrombosis. *Circulation* **83** (6 Suppl), IV-3–14.

Galea, J., Armstrong, J., Gadsdon, P., Holden, H., Francis, S. E., and Holt, C. M. (1996). Interleukin-1β in coronary arteries of patients with ischemic heart disease. *Arterioscler. Thromb. Vasc. Biol.* **16(8)**, 1000–1006.

Glagov, S., Weisenberg, E., Zarins, C. K., Stankunavicius, R., and Kolettis, G. J. (1987). Compensatory enlargement of human atherosclerotic coronary arteries. *N. Engl. J. Med.* **316**, 1371–1375.

Goldsmith, S., Dodge-Brown, D., Katz, A., and Crooks, P. (1989). Differential effect of nicotine on plasma norepinephrine levels in normal humans and in patients with congestive heart failure. *Am. J. Cardiol.* **63(1)**, 122–123.

Grignani, G., Soffiantino, F., Zucchella, M., Pacchiarini, L., Tacconi, F., Bonomi, E., Pastoris, A., Sbaffi, A., Fratino, P., and Tavazzi, L. (1991). Platelet activation by emotional stress in patients with coronary artery diseases. *Circulation* **83**(4 Suppl), II128–136.

Hammond, E. C., and Dorn, D. (1958). Smoking and death rates-report on forty-four months of follow up of 187,783 men. *JAMA*. **166**, 1294–1308.

Hammond, E. C., and Garfinkel, L. (1969). Coronary heart disease, stroke, and aortic aneurism. *Arch. Environ. Health* **19**, 167–182.

Hammond, E. C. (1966) Smoking in relation to the death rates of one million men and women. In *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases* (W. Haenszel, Ed.). National Cancer Institute Monograph No. 19, 127–204. U.S. Department of Health, Education, and Welfare, Bethesda, MD.

He, J., Vupputuri, S., Allen, K., Prerost, M.R., Hughes, J., and Whelton, P. K. (1999). Passive smoking and the risk of coronary heart disease—a meta-analysis of epidemiologic studies. *N. Engl. J. Med.* **340(12)**, 920–926.

Health Survey for England 1994. (1996). (Colhoun and Prescott-Clarke, Eds.) London: HMSO.

Hirayama, T. (1984). Dietary habits in smokers. In *Statistical Methods in Cancer Research*. (W. J. Blot, T. Hirayama, and D. G. Hoel, Eds.). pp.93–94.

Hoffmeister, H. M., Jur, M., Wendel, H. P., Heller, W., and Seipel, L. (1995). Alterations of coagulation and fibrinolytic and kallikrein-kinin systems in the acute and post-acute phases in patients with unstable angina pectoris. *Circulation* **91**, 2520–2527.

Howard, G., Wagenknecht, L. E., Burke, G. L., Diez-Roux, A., Evans, G. W., McGovern, P., Nieto, F. J., and Tell, G. S. (1998). Cigarette smoking and progression of atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA*. **279**, 119–124.

Huber, G. L. (1989). Physical, chemical, and biologic properties of tobacco, cigarette smoke, and other tobacco products. *Sem. Respir. Med.* **10**, 297–332.

Jarvis, M., Russell, M., and Feyerabend, R. (1983). Absorption of nicotine and carbon monoxide from passive smoking under natural conditions of exposure. *Thorax* **38**, 829–833.

Jarvis, M., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C., and Saloojee, Y. (1987). Comparison of tests used to distinguish smokers from nonsmokers. *Am. J. Public Health* **77**, 1435–1438.

Jarvis, M. (1989). Application of biochemical intake markers to passive smoking measurement and risk estimation. *Mutat. Res.* **222**, 101–110.

Jenkins, A., Palausky, A., Counts, R., Bayne, C., Dindal, A. and Guerin, M. (1996). Exposure to environmental tobacco smoke in sixteen cities in the United States as determined by personal breathing zone air sampling. *J. Expo. Anal. Environ. Epidemiol.* **6(4)**, 473–502.

Kahn, H. A. (1966). The Dorn study of smoking and mortality among US veterans: report on eight and one half years of observation. In *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases* (W. Haenszel, Ed.). National Cancer Institute Monograph No. 19, pp. 127–204. U.S. Department of Health, Education, and Welfare, Bethesda, MD.

Koo, L. C., Ho, J. H. C., and Rylander, R. (1988). Life-history correlates of environmental tobacco smoke: a study of nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. *Soc. Sci. Med.* **26(7)**, 751–760.

Kovanen, P. T., Kaatinen, M., and Paavonen, T. (1995). Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* **92(5)**, 1084–1088.

Knutsen, S. F., and Knutsen, R. (1989). The Tromso heart study: Risk factors for CHD and length of education. *Am. J. Epidemiol.* **127**, 923–932.

Larsson, P., Hjemdahl, P., Olsson, G., Egberg, N., and Hornstra, G. (1989). Altered platelet function during mental stress and adrenaline infusion in humans: evidence for an increased activation *in vivo* as measured by filtragometry. *Clin. Sci.* **76(4)**, 369–376.

Larsson, P., Hjemdahl, P., Olsson, G., Angelins, B., and Hornstra, G. (1990). Platelet aggregability in humans: contrasting *in vivo* and *in vitro* findings during sympatho-adrenal activation and relationship to serum lipids. *Eur. J. Clin. Invest.* **20**, 398–405.

Law, M. R., Morris, J. K., and Wald, N. J. (1997). Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ*. **315**, 973–980.

Lazarus, N. B., Kaplan, G. A., Cohen, R. D., and Leu, D. J. (1989). Smoking and body mass in the natural history of physical activity: prospective evidence from the Alameda County study, 1965–1974. *Am. J. Prev. Med.* **5**, 127–135.

Le Marchand, L., Wilkens, L. R., Hankin, J. H., and Haley, N. J. (1991). Dietary patterns of female nonsmokers with and without exposure to environmental tobacco smoke. *Cancer Causes Control* **2**, 11–16.

Libby, P. (1995). Molecular bases of the acute coronary syndromes. *Circulation* **91(11)**, 2844–2850.

Lindsted, K., and Kuzma, J.W. (1990). Husband-wife diet concordance and changes in dietary practices by surviving spouses of cancer cases. *Nutr. Cancer*. **13**, 175–187.

Mackenbach, J. P., Looman, C. W. N., and van der Meer, J. B. W. (1996). Differences in the misreporting of chronic conditions, by level of education:

PM3006532287

Source: https://www.industrydocuments.ucsf.edu/docs/mxgj0001

The effect on inequalities in prevalence rates. *Am. J. Public Health* **86,** 706–711.

Matanoski, G., Kanchanaraksa, S., Lantry, D., and Chang, Y. (1995). Characteristics of nonsmoking women in NHANES I and NHANES I epidemiologic follow-up study with exposure to spouses who smoke. *Am. J. Epidemiol.* **142,** 149–157.

McGill, H. (1988). The cardiovascular pathology of smoking. *Am. Heart. J.* **115,** 250–257.

McGill, H., McMahan, C. A., Malcom, G. T., Oalmann, M. C., and Strong, J. P. (1997). Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. *Arterioscler. Thromb. Vasc. Biol.* 17(1), 95–106.

McKarns, S. C., Smith, C. J., Payne, V. M., and Doolittle, D. J. (1995). Blood parameters associated with atherogenic and thrombogenic risk in smokers and nonsmokers with similar life-styles. *Mod. Pathol.* **8,** 434–440.

Meredith, I. Yeung, A., Weidinger, F., Anderson, T., Uehata, A., Ryan, T., Selwyn, A., and Ganz, P. (1993). Role of impaired endothelium-dependent vasodilation in ischemic manifestations of coronary artery disease. *Circulation.* **87**(suppl V), V56–V66.

Merlini, P. A., Spinola, A., Ardissino, D., Oltrona, L., Broccolino, M., Bortasso, B., Belli, C., and Mannucci, P. M. (1994). Activated factor VII and increased thrombin activity in acute coronary symptoms. *Circulation* **90,** (abstract 964).

Mest, H., Zehl, U., Sziegoleit, W., Taube, C., and Forster, W. (1982). Influence of mental stress on plasma levels of prostaglandins thromboxane B_2 and circulating platelet aggregates in man. *Prostaglandins Leukot. Med.* **8,** 553–563.

Midgette, A. S., Baron, J. A., and Rohan, T. E. (1993). Do smokers have diets that increase their risks of coronary heart disease and cancer? *Am. J. Epidemiol.* **137,** 521–529.

Minnesota BRFSS (Behavioral Risk Factor Surveillance Systems Survey).

Moffatt, R. J., Stamford, B. A., and Biggerstaff, K. D. (1995). Influence of worksite environmental tobacco smoke on serum lipoprotein profiles of female nonsmokers. *Metabolism* **44**(12), 1536–1539.

Molstad, P. (1991). First myocardial infarction in smokers. *Eur. Heart J.* 12, 753–759.

Mueller, H. S., Cohen, L. S., Braunwald, E., Forman, S., Feit, F., Ross, A., Schweiger, M., Cabin, H., Davison, R., *et al.* (1992). Analyses of patient subgroups in the thrombolysis in myocardial infarction (TIMI) trial, phase II. *Circulation* **85,** 1254–1264.

National Health Interview Survey. (1993). Hyattsville, MD: Division of Health Examination Statistics. National Center for Health Statistics.

National Medical Expenditure Survey II. (1987). Agency for Health Care Policy and Research, Rockville, MD.

Netscher, D., Wigoda, P., Thornby, J., Yip, B., and Rappaport, N. (1995). The hemodynamic and hematologic effects of cigarette smoking versus a nicotine patch. *Plast. Reconstr. Surg.* **96,** 681–688.

Nikkila, E. A. (1984). HDL in relation to the metabolism of triglyceride-rich lipoproteins. In *Clinical and Metabolic Aspects of High-Density Lipoproteins.* (N. E. Miller and G. J. Miller, Eds.). Elsevier Science Publishers. Amsterdam.

Ogden, M. W. (1996). Environmental tobacco smoke exposure of smokers relative to nonsmokers. *Anal. Commun.* **33,** 197–198.

Ogden, M. W., Morgan, W. T., Heavner, D. L., Davis, R. A., and Steichen, T. J. (1997). National incidence of smoking and misclassification among the U.S. married female population. *J. Clin. Epidemiol.* **3,** 253–263.

Oliver, M. F. (1989). Cigarette smoking, polyunsaturated fats, linoleic acid, and coronary heart disease. *Lancet* **1,** 1241–1243.

Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. (1990). Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. *JAMA.* **264**(23), 3018–3024.

Perusse, L., Lablanc, C., Tremblay, A., Allard, C., Theriault, G., Landry, F., Talbot, J., and Bouchard, C. (1987). Familial aggregation in physical fitness, coronary heart disease risk factors, and pulmonary function measurements. *Prev. Med.* **16,** 607–615.

Phillips, K., *et al.* (1999). Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Basel by personal monitoring. *Atmos. Env.* **33,** 1889–1904.

Pirkle, J. L., *et al.* (1996). Exposure of the US population to environmental tobacco smoke. The Third National Health Exposure Survey, 1988 to 1991. *JAMA.* **275,** 1233–1240.

Pitillo, R. M., and Woolf, N. (1994). Cigarette smoking as a risk factor for atherosclerosis. *J. Smoking-Related. Dis.* 5(Suppl. 1), 43–47.

Pooling Project Research Group (1978) Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J. Chron. Dis.* **31,** 201–306.

Report of the Scientific Committee on Tobacco and Health (SCOTH). (1998). Environmental tobacco smoke and ischaemic heart disease. London: The Stationary Office. p. 32.

Roberts, W. C. (1989). Atherosclerotic risk factors- are there ten or is there only one? *Am. J. Cardiol.* **64,** 552–554.

Ross, E. M. (1995). Pharmacodynamics: mechanisms of drug action and the relationship between drug concentration and effect. In *The Pharmacological Basis of Therapeutics.* (A. G. Goodman Gilman and L. E. Limbrid, Eds.). pp 29–42. McGraw-Hill, New York.

Rostrup, M., Mundal, H., Kjeldsen, S., Gjesdal, K., and Eide, I. (1990). Awareness of high blood pressure stimulates platelet release reaction. *Thromb. and Haemost.* **63,** 367–730.

Rylander, R., Axelsson, G., Megevand, Y., Dahlberg, C., Liljeqvist, T., and Sundh, V. (1999). Dietary habits for non-smoking females living with smokers or non-smokers. *Eur. J. Public Health* **9,** 142–5.

Scherer, G., Conze, C., Meyerinck, L., Sorsa, M., and Adlkofer, F. (1990). Importance of exposure to gaseous and particulate phase components of tobacco smoke in active and passive smokers. *Int. Arch. Occup. Environ. Health* **62**(6), 459–466.

Schmaier, A. H. (1987). Immunochemical methods to study platelet-associated proteins. In *Modern Methods in Pharmacology* (R. W. Colman and J. B. Smith, Eds.). p. 123. Alan R. Liss, Inc., New York

Schroeder, A. P., and Falk, E. (1995). Vulnerable and dangerous coronary plaques. *Atherosclerosis* **118,** S141–149.

Shibata, A., Sasaki, R., Ito, Y., Hamajima, N., Suzuki, S., Ohtani, M., and Aoki, K. (1989). Serum concentration of beta-carotene and intake frequency of green-yellow vegetables among healthy inhabitants of Japan. *Int. J. Cancer.* **44,** 48–52.

Sidney, S., Caan, B. J., and Friedman, G. D. (1989). Dietary intake of carotene in nonsmokers with and without passive smoking at home. *Am. J. Epidemiol.* **129,** 1305–1309.

Siess, W. (1989). Molecular mechanisms of platelet activation. *Physiol. Rev.* **69,** 58–178.

Smith, C. J., Bombick, D. W., McKarns, S. C., Morton, M. J., Morgan, W. T., and Doolittle, D. J. (1996). Environmental room human physiology study using fresh diluted sidestream cigarette smoke. Proceedings of the 1996 CORESTA Congress, Yokahama, Japan. November 6; pp. 18–36.

Smith, C. J., Morgan, W. T., Doolittle, D. J., Fischer, T. H., Ruppert, T., and Scherer, G. (1998a). Urinary prostacyclin in nonsmokers living with smokers. *Inhal. Toxicol.* **10,** 431–441.

Smith, C. J., and Ogden, M. W. (1998). Tobacco smoke and atherosclerosis progression. *JAMA.* **280,** 32–33.

PM3006532288

Source: https://www.industrydocuments.ucsf.edu/docs/mxgj0001

Smith, C. J., Scott, S. M., and Wagner, B. M. (1998b) The necessary role of the autopsy in cardiovascular epidemiology. *Hum. Pathol.* **29,** 1469–1479.

Smith, C. J., Sears, S. B., Walker, J. C., and DeLuca P. O. (1992). Environmental tobacco smoke: current assessment and future directions. *Toxicol. Pathol.* **20(2),** 289–305.

Smith, C. J., Steichen, T. J., and Fischer, T. H. (1998c). Platelet aggregation in cigarette smokers. *Inhal. Toxicol.* **10,** 765–793.

Sterling, T. D., and Weinkam, J. J. (1990). The confounding of occupation and smoking and its consequences. *Soc. Sci. Med.* **30,** 457–467.

Tanoue, K., Akamatsu, N., Suzuki, H., Katagiri, Y., Yamazaki, H., Fujimoto, T., Fukuda, S., and Onozawa, Y. (1992). Detection of circulating activated platelets by anti-GMP-140 monoclonal antibodies. *Nippon Rinsho.* **50(2),** 330–335.

Thompson, D. H., and Warburton, D. M. (1993). Dietary and mental health differences between never-smokers living in smoking and non-smoking households. *J. Smoking-Related Dis.* **43,** 203–211.

Valkonen, M., and Kuusi, T. (1998). Passive smoking induces atherogenic changes in low-density lipoprotein. *Circulation* **97,** 2012–2016.

Venters, M. H., Jacobs, D. R., Jr., Luepker, R. V., Maiman, L. A., and Gillum, R. F. (1984). Spouse concordance of smoking patterns: the Minnesota heart survey. *Am. J. Epidemiol.* **120,** 608–616.

Wagenknecht, L. E., Burke, G.L., Perkins, L. L., Haley, N. J., and Friedman, G. D. (1992). Misclassification of smoking status in the CARDIA study: a comparison of self-report with serum cotinine levels. *Am. J. Public Health* **82,** 33–36.

Walker, J. C., Polyakov, V., Connell, V. L., Barreto, A. D., Kendal-Reed, M., Howell, M. A., and Smith, C. J. (1999). Predicting real-world responses from odor/irritation psychophysical data: problems encountered and a solution proposed. Poster presented at the 21st Meeting of the Association for Chemoreception Sciences, Sarasota, FL, April 14–18. 1999.

Wang, J., Jen, C., Kung, H., Lin, L., Hsiue, T., and Chen, H. (1994). Different effects of strenuous exercise and moderate exercise on platelet function in men. *Circulation* **90,** 2878–2885.

Whichelow, M. J., Golding, J. F., and Treasure, F. P. (1988). Comparison of some dietary habits of smokers and nonsmokers. *Br. J. Addict.* **83,** 295–304.

Wilson, J. D., and Foster, D. W. (1985). *Textbook of Endocrinology.* 7th edition. Philadelphia, PA: W. B. Saunders Company.

Winslow, C. M., Anderson, R. C., D'Aries, F. J., Frisch, G. E., DeLillo, A. K., Lee, M. L., and Saunders, R. N. (1987). Toward understanding the mechanism of action of platelet activating factor receptor antagonists. In *New Horizons in Platelet Activating Factor Research,* (C. M. Winslow and M. L. Lee, Eds.). pp. 153–157. John Wiley & Sons Ltd.

PM3006532289

Source: https://www.industrydocuments.ucsf.edu/docs/mxgj0001